CARDIOPULMONARY BYPASS, MYOCARDIAL MANAGEMENT, AND SUPPORT TECHNIQUES

THE EFFECTS OF CARDIOPULMONARY BYPASS TEMPERATURE ON NEUROPSYCHOLOGIC OUTCOME AFTER CORONARY ARTERY OPERATIONS: A PROSPECTIVE RANDOMIZED TRIAL

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The effect of systemic perfusion temperature on postoperative cognitive function was investigated in 96 adult patients undergoing elective coronary revascularization with cardiopulmonary bypass at 28° C, 32° C, or 37° C. Neuropsychologic performance was assessed 1 day before the operation and 6 weeks after the operation. Five tests were adapted from the Wechsler Adult Intelligence Scale and two from the Wechsler Memory Scale. *Results*: No patients had major neurologic complications. Ninety-three patients completed the five Wechsler Adult Intelligence Scale tests, but only 70 went on to complete the Wechsler Memory Scale tests as well. In these, there was an effect of cardiopulmonary bypass temperature on the number of neuropsychologic tests in which there was a preoperative to postoperative deterioration ($p = 0.021$), the number with bypass at 37° C being significantly greater than the number with bypass at 32° C ($p = 0.015$). Subsidiary analyses using a multivariate linear model examined the effect of cardiopulmonary bypass temperature on the magnitude of change, with or without allowing for other possible confounding influences. There was an adverse effect of normothermic (37° C) versus moderately hypothermic (32° C) perfusion—more convincingly displayed in the analyses of all seven scores rather than just the Wechsler Adult Intelligence Scale scores. Further cooling to 28° C conferred no additional benefit in terms of cognitive function. The importance of the deterioration is open to question.
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The established practice of using hypothermia in association with cardiopulmonary bypass (CPB) has been challenged recently. However normothermic CPB perfusion exposes a more active brain to potentially lower perfusion pressures and increased use of vasoconstrictors.[1-3] Inconsistencies between assessments of the cerebral effects of normothermic CPB perfusion may be partly because of variation in the techniques of myocardial protection[4-6] and control of temperature and partly because of differences in choice of outcome measure. With improvements in equipment and the management of CPB, gross neurologic deficits are rare isolated catastrophes, not necessarily related to the types of damage that might result from such factors as variation in the perfusion temperature.

The prevalence of "cognitive deficit" has been examined in a number of studies of CPB temperature,[4, 7-12] because it should be more common than neurologic deficit and thus be a more sensitive measure of more subtle gradations of cerebral compromise. Cognitive function has several dimensions, each of which is measurable on a separate scale of measurement in some overall battery of neuropsychologic tests. Cognitive deficit has been variously defined in studies in this area, the effect of all

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definitions being to create a categoric univariate measure out of an outcome that is multidimensional. Underlying each definition is a number of tests that must deteriorate by some specified amount in a battery of a specified size. None of the definitions is any more than a surrogate marker because none has yet been validated against everyday intellectual and psychosocial performance.

The disparity between estimated incidences of "cognitive deficit" may partly reflect laxity of definition but, at an incidence of 30% quoted in 1989, some 35 patients in each limb of a trial would provide 80% power to detect a significant ($p < 0.05$) doubling of incidence by a new intervention. Larger numbers would be needed to detect a halving, or less dramatic changes in either direction, but conventional power calculations have little meaning if one cannot specify a change in outcome measure that is of clinical importance. If the outcome measure is an unvalidated surrogate, clinical importance is impossible to judge.

The principal outcome measure and numbers of patients in this study were determined by pragmatism. The study is a facet of a wider ongoing comparison of the effects of hypothermic (28° C), moderately hypothermic (32° C), and normothermic (37° C) CPB perfusion on function across all organ systems. There were good reasons for aiming for early detection of *any* potentially adverse cerebral effects. The pragmatic constraint was the availability, for only 1 year, of financial support for neuropsychologic testing: this would allow about 100 suitable cases to be recruited and divided among the three temperature groups. This required the surrogate outcome measure to be more sensitive than any of the existing definitions of "cognitive deficit." The logical choice was an index of "cognitive deterioration"—the *number* of deteriorations of score (irrespective of size) in a predetermined number of tests.

At a later stage, it seemed more appropriate to examine the multidimensional outcome with a multivariate statistical analysis that could deal with the magnitudes of the preoperative-to-postoperative score changes rather than simply the numbers of scores that deteriorated. Because this was a post hoc decision, the multivariate analysis could not legitimately be any more than a subsidiary analysis in support of the principal one. It is nevertheless reported in outline because it is the first of its sort in this area of medicine and could well be a useful template for analogous problems in other areas.

Patients and methods

Patients. The study was approved by the Research Ethics Committee of the United Bristol Health Care NHS Trust, and written informed consent was obtained from all patients who took part. Ninety-six patients undergoing primary elective or urgent myocardial revascularization were recruited after prospective exclusion of patients with previous neurologic disease or psychiatric illness. A random number table was used to allocate patients to receive CPB perfusion at 28° C (hypothermia), 32° C (moderate hypothermia), or 37° C (normothermia).

Preoperative assessment and baseline measurements. The preoperative assessment included all of the usual clinical and investigational measures, and the general level of risk that they presented for cardiac operations was expressed in terms of the New York Heart Association classification and Parsonnet score.[13] A detailed neurologic examination was also carried out. Patients more than 54 years old with a cervical bruit or who were otherwise at major risk of carotid arterial disease by the criteria of Berens and associates[14] were screened for underlying extracranial vascular disease with an ATL MK 600 scanner (Advanced Technology Laboratories, Hertfordshire, United Kingdom) with a 7 and 5 MHz mechanical sector transducer (UM9 HDI).

The baseline neuropsychologic assessment was carried out on the day before the operation and consisted of an initial battery of five neuropsychologic tests taken from the revised Wechsler Adult Intelligence Scale (WAIS) and an additional two tests from the Wechsler Memory Scale (WMS).[15] These are accepted tests of global cognitive function. The tests were presented in a fixed order according to conventional practice and the scores were arranged so that larger scores indicated better neuropsychologic performance.

<u>WAIS</u>
1. Digit Span
2. Picture Arrangement
3. Block Design
4. Object Assembly
5. Digit Symbol

<u>WMS</u>
6. Verbal Paired Associates
7. Visual Paired Associates

In addition, because cognitive function may be influenced by mood,[16] each patient's current mental health was also assessed by means of the General

Health Questionnaire (GHQ-30)[17] and Hospital Anxiety and Depression Scale (HAD).[18]

Anesthetic and surgical technique. Anesthesia, CPB, and surgical technique were standardized as far as possible. Anesthesia was induced with thiopental sodium (1 to 3 $mg \cdot kg^{-1}$) and fentanyl (3 to 5 $\mu g \cdot kg^{-1}$) and was maintained by volatile agents delivered in a 50% air/oxygen mixture in a pulmonary ventilator adjusted to maintain normocapnia. Pancuronium bromide (0.1 to 0.15 $mg \cdot kg^{-1}$) provided neuromuscular blockade, and anticoagulation was with heparin to a target activated clotting time of 480 seconds. For CPB, a standard circuit took blood from the right atrial appendage through a two-stage cannula and returned it to the ascending aorta: it consisted of polyvinyl chloride tubing (Sorin Biomedica UK Ltd., Midhurst, United Kingdom), a Cobe roller pump (Cobe Laboratories, Inc., Lakewood, Colo.), a hollow-fiber membrane oxygenator, and a 40 μm arterial line filter (Sorin Biomedica Cardio, Saluggia, Italy). The extracorporeal circuit was primed with 1000 ml of Hartmann's solution, 500 ml of urea-linked gelatin plasma substitute (Gelofusine; B. Braun Medical Ltd., Emmenbrücke, Switzerland), 60 mg of heparin, and 0.5 $gm \cdot kg^{-1}$ of mannitol. Nasopharyngeal temperature monitoring was used to direct management of CPB perfusion temperature, patients in the normothermic group requiring active warming throughout the period of CPB. The perfusion was nonpulsatile and the flow rate was adjusted according to the nasopharyngeal temperature; flow rate was 2.4 $L \cdot m^{-2} \cdot min^{-1}$ for the normothermic group, decreasing 2.0 and 1.8 $L \cdot m^{-}2 \cdot min^{-1}$ (respectively) once the target temperatures had been reached in the moderately hypothermic and hypothermic groups. Phenylephrine was used to maintain mean systemic perfusion pressures at 50 to 60 mm Hg. An infusion of propofol (3 $mg \cdot kg^{-1} \cdot hr^{-1}$) provided anesthesia, and alpha-stat acid-base management was used throughout CPB. The strategy for myocardial protection was based on electromechanical arrest with antegrade cold crystalloid cardioplegia and topical cooling with 0.9% sodium chloride solution at 4° C. One liter of St. Thomas' Hospital I cardioplegic solution was given initially. This infusion was followed by 300 ml for every 30 minutes of aortic crossclamping, or more frequently if electrical activity returned. Distal anastomoses were completed during a single period of aortic crossclamping. Proximal anastomoses were completed with the heart beating and with partial aortic occlusion.

Rewarming in the nonnormothermic groups began as soon as the distal anastomoses were completed, with a temperature difference of 8° C between the blood in the heat exchanger and the rewarming fluid. CPB was discontinued only after full rewarming to 37° C, and the blood remaining in the circuit was reinfused into the patient via a 40 μm filter (SQ40S, Pall Europe Ltd., Portsmouth, United Kingdom). Blood loss was replaced in the first instance with autologous blood predonated after induction of anesthesia.

After the procedure, patients were cared for in the cardiac surgical intensive care unit. A standardized protocol was used to wean them from their initial respiratory support, which consisted of controlled ventilation, inspired oxygen therapy, and positive end-expiratory pressure. They were extubated when fully rewarmed, alert, and hemodynamically stable.

Postoperative assessments. Patients were examined for gross neurologic deficit on the morning after the operation and underwent full neurologic examination on day 4, when fully mobile and receiving only minimal oral analgesia. Six weeks after the operation, patients were subjected again to the same battery of neuropsychologic tests that they had completed before the operation.

Statistical methods. The analyses used the procedures available in the SAS statistical software package (SAS Institute, Inc., Cary, N.C.) on the departmental microcomputer.

Kruskal-Wallis testing was used to test the null hypothesis that there was no overall temperature-related difference in the principal outcome measure—the number of tests per patient in which there was a deterioration between the preoperative baseline and the 6-week postoperative score: this was followed by Mann-Whitney U tests with Bonferroni correction for differences between individual temperature groups.

The magnitudes of score change for each of the neuropsychologic tests were dealt with in a subsidiary multivariate analysis. This was preceded by repeated-measures analysis of variance (GLM procedure) on each test taken *one at a time*: these examined preoperative-to-postoperative score change within patient and differences in score change between groups, but this was only to illustrate the limited resolving power of a conventional univariate analysis. The multidimensionality of the outcome was checked by a principal component analysis, and then a multivariate analysis was under-

Table I. *Preoperative characteristics*

Characteristic	*28° C (n = 31)*	*32° C (n = 36)*	*37° C (n = 29)*
Age (yr)	57.3 ± 1.6	60.7 ± 1.4	58.7 ± 1.5
Sex (M/F)	27/4	30/6	27/2
BSA (m^2)	1.91 ± 0.03	1.92 ± 0.04	1.94 ± 0.04
NYHA			
I and II	18	15	18
III and IV	13	21	11
Parsonnet score	1.42 ± 0.44	3.28 ± 0.62	1.76 ± 0.43
Elective/urgent	24/7	26/10	23/6
Hypertension	11	15	10
Diabetes	1	2	1
PVD	1	1	3
GHQ	33.4 ± 2.7	33.7 ± 2.5	35.1 ± 2.4
HAD Anxiety	7.9 ± 0.7	7.2 ± 0.8	7.5 ± 0.7
HAD Depression	5.2 ± 0.7	4.5 ± 0.5	5.4 ± 0.5

Data are expressed as mean ± standard deviation. *BSA,* body surface area; *PVD,* peripheral vascular disease.

Table II. *Intraoperative and postoperative characteristics*

Characteristic	*28° C (n = 31)*	*32° C (n = 36)*	*37° C (n = 29)*
No. of grafts	3.1 ± 0.2	2.8 ± 0.15	3.3 ± 0.19
CPB time (min)	80.4 ± 3.6	74.9 ± 3.9	85.8 ± 4.4
Crossclamp time (min)	39.3 ± 2.5	34.2 ± 2.0	40.7 ± 2.0
Phenylephrine (μg)	2200 ± 340	2800 ± 430	5300 ± 1200
Inotropic support*			
A	21	24	16
B	8	6	10
C	2	2	3
Requirement for IABP	0	4	0
Period of intubation (hr)	8.3 ± 1.1	10.7 ± 2.0	12.8 ± 2.1
Reopened for bleeding	1	1	2
Intensive care stay (hr)	26.8 ± 4.3	29.1 ± 3.5	26.1 ± 2.9
Postop. hospital stay (days)	6.9 ± 0.2	7.4 ± 0.3	8.1 ± 0.7

Data are expressed as mean ± standard deviation. *IABP,* Intraaortic balloon pump.
**A,* None; *B,* dopamine ≤ 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$; *C,* dopamine >3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and/or any other inotropic agent.

taken to examine for temperature-related differences in effect across all tests *considered together,* while allowing to different degrees for possible confounding effects of other explanations. Multivariate linear models were created by means of the multiple response multiple regression statement (MTEST) in the regression procedure (REG).

The statement first standardized between-patient variability in score change across all tests by expressing each score change in units of its standard deviation about its mean overall temperature groups. The intermediate CPB temperature (32° C) was made the reference state, and two "dummy variables" were created to allow description of differences from reference at the other two CPB temperatures. (Both dummy variables were set at zero for patients who underwent CPB at 32° C; for 28° C, one was set to 1 and the other to 0, and vice versa for 37° C.) A set seven multiple regressions were then used to estimate the regression coefficients of each dummy variable as indications of differences (from reference) in effect on the standardized variability of each score change taken one at a time. The set of seven pairs of regression coefficients for the two temperature dummy variables was then examined by multivariate testing of the null hypothesis that neither 28° C versus 32° C nor 37° C versus 32° C had any overall effect across all score changes taken together.

In the exploration of possible confounding by other influences on score change, a preliminary multivariate analysis of variance was carried out on the preoperative and 6-week postoperative scores for GHQ, HAD Anxiety, and HAD Depression. For the exploration proper, three parallel versions were carried out of the multivariate analysis described in the preceding paragraph. In the first, no allowance was made for confounding: the regression coefficients of the temperature dummy variables were estimated in multiple regressions that contained no additional explanatory variables. In the second, allowance was made for all possible recorded confounders (patients' characteristics, physical health, psychologic health, preoperative cognitive function, conduct of the operation, and the preoperative-to-postoperative changes in general mental health, anxiety, and depression). In the third, allowance was made for a selection of 11 potentially more likely confounders chosen by a preliminary series of stepwise multiple regressions that included variables in which there was 80% confidence of explanatory effect on at least one score.

Results

Thirty-one patients received CPB at 28° C, 36 at 32° C, and 29 at 37° C. The patients' characteristics and descriptors of physical and mental health are summarized in Table I. No patient had a carotid stenosis greater than 50% on duplex scanning and there were no intergroup differences in degree of stenosis. The intraoperative and postoperative characteristics are summarized in Table II. The left internal thoracic artery was used in 96% of patients

Table III. *Distributions of preoperative and postoperative neuropsychological scores*

CPB temperature	Digit Span	Picture Arrangement	Block Design	Object Assembly	Digit Symbol	Verbal Paired Associates	Visual Paired Associates
28° C							
Missing	—	—	—	—	—	6	8
Preop.	14.2 ± 3.1	12.2 ± 4.9	32.1 ± 7.4	30.0 ± 5.6	41.9 ± 9.8	16.2 ± 3.4	12.1 ± 3.5
Six weeks	14.4 ± 3.8	12.4 ± 4.0	31.6 ± 9.0	30.5 ± 4.1	43.4 ± 9.6	16.0 ± 4.0	13.6 ± 3.3
Score change	0.20 ± 2.9	0.2 ± 5.6	−0.5 ± 5.7	0.5 ± 3.9	1.5 ± 4.0	−0.2 ± 3.9	1.5 ± 4.7
32° C							
Missing	1	1	1	—	—	5	8
Preop.	14.1 ± 4.1	13.3 ± 4.9	28.1 ± 11.5	27.2 ± 7.0	39.2 ± 11.0	16.0 ± 3.8	12.9 ± 3.3
Six weeks	14.2 ± 4.5	12.1 ± 5.7	29.7 ± 11.8	28.7 ± 5.3	42.6 ± 12.0	15.6 ± 4.1	12.0 ± 4.5
Score change	0.11 ± 2.7	−1.2 ± 4.0	1.6 ± 5.9	1.5 ± 4.6	3.4 ± 5.1	−0.4 ± 3.7	−0.9 ± 4.6
37° C							
Missing	—	1	—	—	—	5	8
Preop.	15.4 ± 4.3	14.0 ± 5.0	33.3 ± 8.6	29.1 ± 5.9	42.8 ± 11.4	17.5 ± 3.3	13.0 ± 3.7
Six weeks	14.6 ± 3.9	12.6 ± 5.2	32.3 ± 11.1	28.9 ± 7.0	43.8 ± 10.9	16.1 ± 3.8	12.9 ± 4.5
Score change	0.8 ± 3.0	−1.4 ± 5.2	−1.0 ± 7.1	−0.2 ± 5.6	1.0 ± 5.6	−1.4 ± 4.6	−0.1 ± 3.8

Date are expressed as mean scores ± standard deviation.

overall. One death occurred on the third postoperative day (in a patient who had undergone hypothermic CPB) during emergency reintubation for respiratory failure.

In the neurologic examinations on the fourth postoperative day, a positive grasp reflex was elicited in five patients (two after 28° C, one after 32° C, and two after 37° C), and a positive Babinski reflex was elicited in eight patients (two after 28° C, four after 32° C, and two after 37° C). Five patients had a sensory deficit in the C8 and T1 dermatomes of the left hand (the same side as the dissection of the internal thoracic artery); one of them also had muscle weakness and one still had radicular pain at 6 weeks. In the testing of general mental health 6 weeks after the operation, there was an overall improvement in scores for GHQ, HAD Anxiety, and HAD Depression (multivariate analysis of variance, $p = 0.0001$) but the degree of improvement was not temperature related.

Neuropsychologic assessment. Table III shows the means and standard deviations of the preoperative and 6-week postoperative scores in each of the neuropsychologic tests. With one exception, the seven repeated-measures analyses of variance were unable to identify a significant effect of repetition (preoperative-to-postoperative) or temperature group, or the interaction between them: for Digit Symbol there appeared to be a preoperative-to-postoperative improvement in score in the moderately hypothermic group, but this needs to be qualified by the observations that it was one "significant" result in seven inferential tests and that the preoperative score in the patients who received CPB perfusion at 32° C was appreciably lower than in the other two groups. Univariate analysis of magnitude of score change was not convincingly able to resolve any differences that there may have been.

Table III also indicates that there were missing values in a number of tests, principally those for verbal and visual paired associates, which were the last to be presented. The result was that, of the 96 patients studied, there were 93 who provided complete sets of scores for the first five tests, but only 70 who completed all seven tests. The number of patients who could be included in the most complete analysis was therefore reduced to 70.

Analysis of principal outcome measure: numbers of deteriorations. Fig. 1 shows three superimposed bar histograms of distributions, by temperature group, of numbers of patients in whom there was deterioration in from zero to seven tests in 70 patients. The distributions of patients across numbers of deteriorations differed ($p = 0.021$, Kruskal-Wallis), with the number of deteriorations being greater after normothermic than after moderately hypothermic CPB ($p = 0.015$, Mann-Whitney test with Bonferroni correction). A parallel analysis of the 93 patients who provided five complete sets of scores also indicated an overall temperature effect ($p = 0.029$) and a difference ($p = 0.03$) between normothermic and moderately hypothermic CPB perfusion.

Multivariate analysis of magnitude of score change. Table IV shows the estimates of the regression coefficients of the dummy variables for CPB at

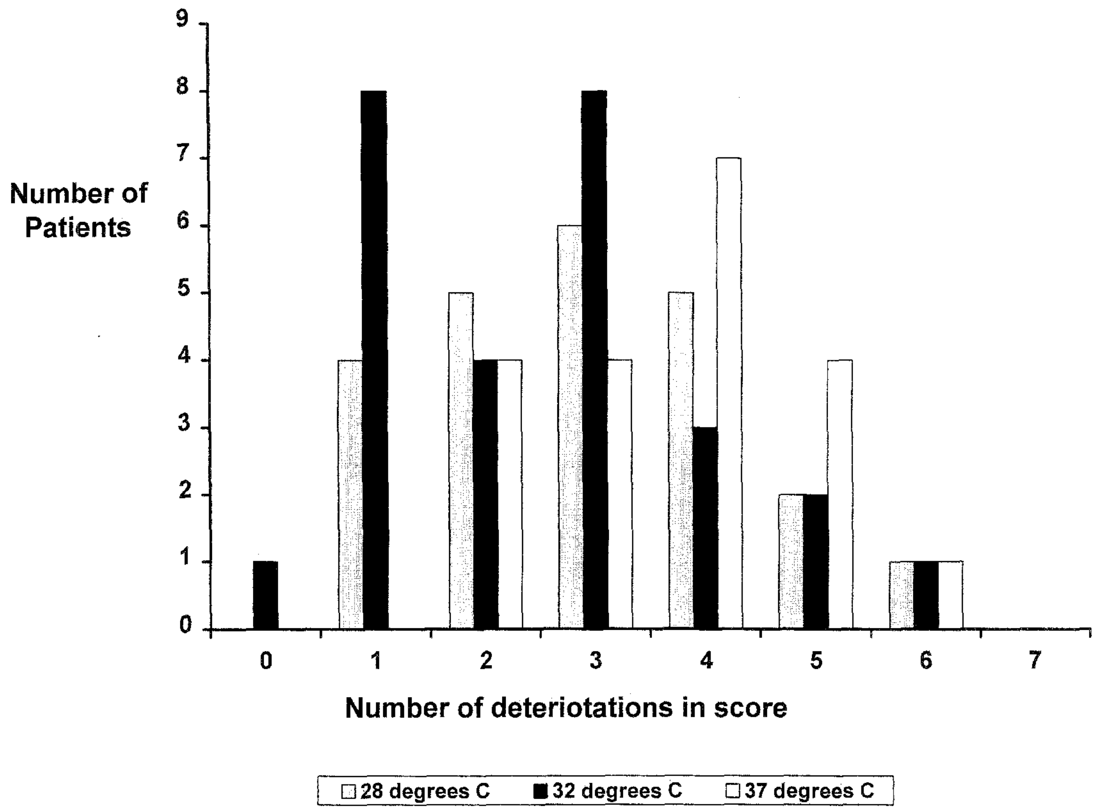

Fig. 1. Superimposed bar histograms of the numbers of patients in the three CPB temperature groups who showed preoperative-to-postoperative deteriorations in from zero to six of the seven neuropsychologic tests.

28° C versus 32° C (upper section) and 37° C versus 32° C (lower section) for the regressions on the standardized variabilities of each of the seven neuropsychologic tests in turn, comparing the effects of making no allowance, selective allowance, or unselective allowance for confounding by other measured variables. The three estimates for each score in each section tend to be similar, with the estimates in the lower section being more negative than the estimates in the upper section. The p values at the end of each line are the probabilities that the estimates on each line do not differ collectively from zero. They offer less than 95% confidence in any suggestion that the effects of hypothermic CPB perfusion differ from those of moderately hypothermic perfusion, but suggest with more than 95% confidence that the effects of normothermic CPB perfusion differ from those of moderately hypothermic perfusion. The predominantly negative signs of the regression coefficients in the lower section of Table IV indicate that the scores tended overall to deteriorate more with normothermia than with moderate hypothermia, which was consistent with the results of the simpler analysis of the principal outcome measure.

In a similar parallel analysis of the five scores in 93 patients, temperature effects were identified with less confidence: a difference with $p < 0.05$ between 37° C and 32° C was apparent only in the model in which selective allowance was made for confounding. More resolving power seemed to have been lost by having to omit the last two neuropsychologic tests than had been gained by being able to include 23 more patients.

Discussion

Warm heart surgery, defined as the use of continuous warm blood cardioplegia and normothermic bypass, was a concept introduced in the late 1980s after Lichtenstein and associates[19] suggested that myocardial oxygen consumption at 37° C was reduced by 90% by electromechanical arrest alone, and that the additional reduction by hypothermia was only 5% to 7%. Although there is some evi-

Table IV. *Regression coefficients for temperature dummy variables in regressions with differing allowance for confounding*

Allowance for Confounders	*Digit Span*	*Picture Aggangement*	*Block Design*	*Object Arrangement*	*Digit Symbol*	*Verbal Paired Associates*	*Visual Paired Associates*	*p Value from Wilks lambda*
28° C versus 32° C								
None	−0.03	0.80	−2.76	−1.82	−2.64	0.03	2.39	0.092
Selective	−0.26	0.80	−3.53	−1.93	−2.74	−0.39	0.71	0.071
Nonselective	−0.74	0.65	−3.66	−1.37	−2.93	−0.33	1.25	0.158
37° C versus 32° C								
None	−1.38	−0.20	−2.62	−3.50	−3.24	−0.83	0.79	0.033
Selective	−1.76	−0.07	−4.30	−3.25	−3.10	−2.14	0.87	0.003
Nonselective	−1.92	0.033	−3.61	−3.34	−3.34	−2.12	0.89	0.012

dence in favor of warm blood *cardioplegia* rather than conventional hypothermic techniques, particularly for high-risk subgroups,[20, 21] there may be disadvantages to combining this with normothermic *systemic* perfusion. The lower systemic vascular resistance and increased requirement for vasoconstrictors[1-3] during normothermic perfusion carries a theoretical risk of injury to the warm, metabolically active brain. Martin and colleagues[4] carried out a randomized trial of warm blood cardioplegia and systemic normothermia (≥35° C) versus cold crystalloid cardioplegia and hypothermic perfusion (≤28° C): they demonstrated a significantly higher stroke rate in the normothermic group (3.1% vs 1.0%, respectively). The solution used for blood cardioplegia caused elevated blood glucose in the normothermic group, and this was a possible confounder because there is evidence that the brain is more susceptible to ischemic injury during hyperglycemia.[22] However, no significant confounding effect of blood glucose could be identified in a subsequent multifactorial analysis of the original data from the randomized study.[23] Another criticism was that the normothermic group received large volumes of retrograde cardioplegia, whereas the hypothermic group received only antegrade cardioplegia. Becker, Rich, and Reed[24] suggested that retrograde cardioplegia may flush particles of atheromatous debris from the coronary arteries into the ascending aorta and that these may embolize to the brain on removal of the crossclamp. In a recent study with extracranial ultrasonography, microembolic events were significantly more frequent after warm retrograde cardioplegia than after antegrade techniques at any temperature.[25] In a subsequent observational study, Craver and coworkers[5] compared 379 coronary revascularizations using hypothermic retrograde blood cardioplegia and hypothermic perfusion (29° C to 33° C) with retrospective control procedures using warm retrograde blood cardioplegia and normothermic perfusion. Q-wave infarction or death was just as prevalent in the normothermic procedures although the patients were nominally at lower risk in terms of age, severity of angina, and incidence of previous coronary surgery, and postoperative neurologic events was significantly more prevalent (4.7% vs 1.8%), thus intensifying concerns about adverse cerebral effects of normothermic perfusion. By contrast, Singh and colleagues[6] found no significant difference between the incidence of neurologic complications in 2585 consecutive patients in whom cold antegrade crystalloid cardioplegia was combined with actively maintained normothermic CPB perfusion and 1605 retrospective control subjects undergoing hypothermic perfusion (25° to 30° C).

In the present study, no patient had major neurologic complications. The minor signs that did occur were unrelated to perfusion temperature. Meticulous care was taken to exclude patients with previous strokes or transient ischemic attacks, and none of the patients who underwent carotid duplex investigation had a carotid stenosis greater than 50%. This careful selection may well have reduced the overall susceptibility to cerebral complications in the sample.

Neuropsychologic outcome has been studied by a number of workers[7-12] as a more sensitive indication of cerebral compromise than frank neurologic deficit and more suited to detecting subclinical deficits in cognitive function that might follow cardiac operations. Martin and associates[4] undertook a subgroup analysis of 150 of the patients in their study who underwent neuropsychologic assessment: they found no significant difference between those who underwent normothermic as opposed to hypothermic perfusion. Wong and colleagues,[9] in a small prospective randomized study, found no evidence of cerebral protection or improved neuropsychologic outcome after hypothermic perfusion. Similarly, McLean and coworkers[10] found no temperature-related difference in 153 patients who completed a neuropsychologic profile after being randomly allocated to receive either warm (>34° C) or cold (≥28° C) CPB perfusion.

Wechsler was the first to suggest that a deterioration by one standard deviation in scores for more than one test might be associated with cognitive deficits important enough to impair quality of life after head injury. His complete battery included a larger number of tests than have the adaptations to cardiac surgery, and his suggestion was never formally validated against everyday cognitive performance. A universally applicable threshold for declaring "deficit" is likely to be meaningless: some patients who make heavy use of their cognitive faculties may be distressingly aware of small deteriorations in performance that would go completely undetected by others who make more limited demands on their intellect.

The definitions of "cognitive deficit" that have so far been used in relation to cardiac surgery lack standardization in what constitutes a deficit and how soon after the operation it should be assessed, although there has been a suggestion that deficits found 2 months after the operation persist for at least a year.[12] Some workers have designated a "neuropsychologic" deficit as a deterioration from baseline by one standard deviation in two or more tests, and others as a deterioration by 20% of the baseline value, but the total number of tests in the battery has not been standardized. Deviation by one standard deviation would have given an incidence of 15 deficits in the 70 patients in this study who completed seven tests, but only seven deficits in the 93 who completed five tests. Deterioration by 20% would have given an incidence of 27 of 70 or 16 of 93, whereas a definition based on *any* deterioration in two tests would have given an incidence of 57 of 70 or 53 of 93. The principal outcome measure in this study retained more of the available information than any of these definitions and provided more discriminating power for temperature-related differences. The testing at 6 weeks in this study was intended to reduce effects of retained learning by repetition and short-term postoperative deficits.

The subsidiary post hoc multivariate analysis supported the simpler principal analysis. It also gave a clearer indication of the importance of including the two tests from the Wechsler Memory Scale, which are known to be more sensitive to the more labile aspects of cognitive function. It was also more sensitive to temperature-related effect than was the blunter instrument of multiple univariate analyses of the magnitudes of score change. The form of analysis was chosen from what was available and reasonably user-friendly in the commercial packages existing in-house and which could readily be applied to analogous problems of similar form. It was relatively conservative and robust, but more elaborate procedures run on out-of-house computers may well have been able to deal more effectively with missing values and bring more resolving power to the interesting observation that CPB perfusion at 28° C was, if anything, more deleterious to cognitive function than that CPB perfusion at 32° C.

All the existing measures of cognitive deficit and the measures of cognitive deterioration used in this study are no more than surrogate markers. If the choice has to be between arbitrary outcome measures that are all surrogates, there seems little reason not to choose the most sensitive. Surrogate measurement may be disparaged as "measuring the unimportant when the important cannot be measured." Its conventional justification in clinical research is that it may indicate an iceberg of potential morbidity that may well have a tip of some important size, especially in an activity with a large turnover. There are strong arguments for paying some attention to deterioration in *any* surrogate measure of something as important as cerebral function in the large numbers of patients worldwide who undergo CPB. This is particularly so if a greater deterioration seems to be associated with a proposed change from a more generally established practice, such as the use of hypothermia during CPB.

Conclusion

This study has demonstrated a deleterious effect of normothermic CPB on cognitive function, with no obvious added benefit from lowering perfusion temperature further than 32° C. The absence of any advantages in nonneurologic measures of outcome, such as intubation time, reopening for bleeding, intensive care, and postoperative hospital stay, provide little incentive to recommend the routine use of normothermic systemic perfusion.

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Commentary

Regragui's and colleagues[1] from Bristol, United Kingdom, report that hypothermia is safer for the brain than normothermic perfusion on the basis of a prospective, controlled study. This is an important conclusion for those who are weighing the evidence to choose what temperature to maintain during cardiopulmonary bypass (CPB) in coronary operations.

The long-standing practice of using hypothermia during routine CPB was challenged by Lichtenstein and colleagues[2] in a letter to *The Lancet,* in which they described an operation with a 6½-hour long crossclamp time in a 64-year-old woman. She died of hemorrhage 17 hours afterward but had good cardiac function in the meantime, attributed by the authors to warm myocardial perfusion. Lichtenstein and colleagues[3] subsequently published a retrospective series in which a group of patients having normothermic CPB seemed to do better than a historical comparison group. Writing as the "Warm Heart Investigators,"[4] they returned to *The Lancet* with a prospective randomized trial of surgery at 33° to 37° C or 25° to 30° C in 1732 patients. There was no significant difference in mortality ($p = 0.12$), or myocardial infarction, but there was less enzyme leakage in the warmer group. In another prospective randomized trial of warm (>35° C) versus hypothermic (<28° C) CPB in 1001 patients, Martin and colleagues[5] from Emory University found no difference in the cardiac outcome. These two prospective randomized trials, including 2733 patients, give lukewarm support, at most, for a return to normothermic CPB.

Not only did the Emory trial data fail to show cardiac benefit, but they revealed a worrying excess of stroke. There were three times as many neurological events, 22 versus seven ($p < 0.005$), predominantly caused by perioperative stroke. Note that the overall prevalence of perioperative cerebrovascular accidents in the Emory trial of 1001 cases was 2%. This is important in designing a study, because in trials of about 100 patients, such as that reported by the Bristol group, a total stroke count of anything between zero and seven would be compatible with chance (based on the 95% confidence limits of 2/100).[6] Stroke as an outcome cannot be used in a study of this size. In fact, to design a prospective randomized clinical trial to seek a difference at the level that Martin and associates found (3% vs 1%), a power calculation[7] indicates that 1030 patients would be needed in each group (alpha 5%, beta 10%) to avoid a "beta error."

Regragui and associates[1] chose to use neuropsychology as their outcome measure. Thus first we must address the question of the clinical relevance of these tests. Can neuropsychologic testing be used as a surrogate to allow us to draw inference about stroke risk, but with much smaller numbers? I think not. I distinguish between focal infarction and global injury.[8] The etiology is different and therefore the means of prevention. The ideal perfusion strategy to minimize global cerebral impairment will not prevent an occasional stroke caused by a mechanical problem. Conversely, a group of young nonatheromatous patients are highly unlikely to have focal deficit, but might be globally obtunded by some ill-conceived CPB technique. Global cerebral injury may be ameliorated by attention to the detail of perfusion strategy, and it is this which is best discerned by neuropsychologic tests.

Which of the variety of neuropsychologic tests available have most validity as markers of CPB-related cerebral damage? An international group of experts, representing the relevant disciplines, have written a consensus statement on neurobehavioral outcomes after cardiac surgery.[9] It would seem reasonable for new researchers in the field to indicate their awareness of previous work and to use established methods. This avoids "reinventing the wheel." If there are good reasons to deviate, these should be explicitly stated and cogently defended. This applies not only to which tests are used, but also to how the results are analyzed. In early studies of the prevalence of cerebral injury, individuals were defined as having, or not having, a "deficit" on the basis of a drop of one standard deviation.[10] A number of criteria might be applied, and these have been meticulously reviewed.[11] On the other hand, when neuropsychologic tests are used to compare one method with another, we need no longer make arbitrary decisions about whether an individual does or does not have a deficit. Instead, we can look at change and its relative difference between groups, which greatly enhances the power of the analysis.[12, 13] The pitfall is that the data can be analyzed in a number of different ways: counts of patients with or without deficit, those whose scores go down (or up), the number of tests that change, summary statistics of raw scores, difference in pooled or amalgamated scores, and any combination or permutation of these. The temptation is to look at the test data in several ways but only to report the statistical method that produced significant difference. It is better if the criteria, and the method of analysis, are stated ahead of time and the results of all analyses reported.

Surgeons have been harshly taken to task for failing to perform proper research by the Editor of *The Lancet,* who titled a recent editorial "Surgical Research or Comic Opera."[14] In my view this slur was not deserved, but only by doing good clinical studies will we shake off this reputation for poor science. We need to evaluate uncertainties with properly conducted prospective randomized trials. Surgeons should be aware of the statistical requirements to perform trials of adequate power. Methods should be well validated, based on established practice within our own and other scientific disciplines, and statistical analyses should be well planned and appropriate to the task. Although I prefer hypothermia to normothermia, with these standards in mind, I would not rely on the Bristol paper for proof that hypothermia protects the brain better than warm CPB.

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